REMARKS

This response addresses the issues raised by the Examiner in the Office Action mailed October 17, 2006. Claims 44, 70, 83-118 and 129 have been canceled. Claims 45 and 71 have been amended to reflect the cancellation of claims 44 and 70, upon which claim 45 and 71 depend, respectively.

Reply to 35 U.S.C. § 112, First Paragraph Rejections

The Examiner rejected claims 44, 70, 87, 97, 106, 114 and 129 under 35 U.S. C. § 112, first paragraph. Specifically, the Examiner contends that the claims fail to comply with the written description requirement since they insert new matter.

In response, Applicant has obviated the Examiner's rejection by canceling claims 44, 70, 87, 97, 106, 114 and 129.

The Examiner also rejected new claims 83-118 under 35 U.S. C. § 112, first paragraph, because the specification does not reasonably provide enablement for a method of providing chemotherapeutic treatment for any type of cancer using any chemotherapeutic agent.

In response, Applicant has obviated the Examiner's rejection by canceling claims 83-118.

Reply to 35 U.S.C. § 103 Rejection

The Examiner rejected currently pending claims 40-43, 45-69, 71-82 and 119-128, in light of Hudis et al. combined with Henderson et al., under 35 U.S.C. § 103(a). Applicant respectfully overcomes this rejection for the following reasons.

Hudis et al. discloses a sequential and dose-dense treatment regimen for breast cancer consisting of 3 cycles of doxorubicin 90 mg/m^2, followed by 3 cycles of paclitaxel 250 mg/m^2, and finally 3 cycles of cyclophosphamide 3 g/m^2. P. 18, col. 1. Henderson et al. discloses concurrent administration of cyclophosphamide 600 mg/m^2 plus

doxorubicin 60, 75 or 90 mg/m^2, followed either by no paclitaxel or paclitaxel 175 mg/m^2.

According to the M.P.E.P., "it is improper to combine references where the references teach away from their combination." *See* Section 2145, citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). Hudis et al. expressly teaches away from the lower dosage regimens disclosed in Henderson et al. and the specification. Specifically, Hudis et al. notes that "[c]ombined with new drug discovery, dose escalation and intensification of the known active adjuvant therapy agents represent the likeliest route to improved survival from resected breast cancer," and that "the dose reductions of doxorubicin required to allow simultaneous therapy with paclitaxel or other agents may compromise effectiveness." P. 21, col. 2. (Emphasis added). Hudis et al. adds that "[o]n retrospective and prospective analyses, dose intensification has been associated with improved outcomes, and a pilot study suggests that patients with 10 or more positive nodes may benefit from very-high dose therapy." P. 18, col. 2.

Moreover, according to Applicant,

> before INT C9741 [the basis for the claimed invention], the expectation was that dose escalation of adjuvant therapy agents represented the likeliest route to improved survival from resected breast cancer and that dose reductions would compromise the effectiveness of the treatment.
>
> The results of INT C9741 were, thus, remarkable and unexpected in that reduced doses of adjuvant therapy agents, given sequentially and in a dose-dense regimen, resulted in efficacious treatment.
>
> Although the reduced doses disclosed in Henderson et al. were efficacious, there was no expectation, reasonable or otherwise, that those reduced doses, used in a sequential and does-dense regimen, would be efficacious. Under the medical ethics principle of equipoise, if the doses disclosed in Henderson et al. were more likely than not to be efficacious in a sequential and dose-dense regimen, proceeding with INT C9741 would have been unethical. The principle of equipoise stands for the proposition that a subject should only be submitted to a randomized, controlled experiment if there is substantial uncertainty

> about whether a treatment would benefit the subject. In mathematical terms, equipoise requires that, prior to a study, the probability for either treatment A or treatment B being superior to the other is 50%.
>
> Indeed, if the doses disclosed in Henderson et al. were more likely than not to be efficacious in a sequential and dose-dense regimen, the National Cancer Institute would never have allowed the INT C9741 study to go forward.

Declaration of Larry Norton M.D. ¶¶ 8-11 (attached hereto).

Henderson et. al examined the clinical efficacy of concurrently administered cyclophosphamide 600 mg/m^2 and doxorubicin 60, 75 or 90 mg/m^2. There would be no expectation of success that cyclophosphamide and doxorubicin administered sequentially, as in the claimed invention, at those doses would yield a similar clinical outcome. *See* Declaration of Larry Norton M.D. ¶ 10. At best, the Henderson et al. would make the claimed method obvious to try. "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). "'[O]bvious to try' is not the standard under § 103." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

The Examiner also contends that Henderson et al. is not necessary to repair the defect in the teaching of Hudis et al. and render the instant claims obvious. Final Office Action at p. 14. Specifically, the Examiner argues that "discovering that the lower dosages disclosed in the instant claims are equally effective is, by Applicant's own reasoning, merely routine and ordinary experimentation which is therefore obvious over the prior art." *Id.*

Applicant respectfully points out that the claimed invention requires the administration of "well-tolerated" amounts of chemotherapeutic agents, and while the establishment of a dose response curve for a particular chemotherapeutic agent may be routine in the art, the use of an optimal amount of a chemotherapeutic agent in a

sequential and/or dose dense regimen with other agents may not necessarily result in a successful clinical result due to factors such as unexpected toxicities, unexpected interactions of the agents and feasibility in terms of detrimental impact on the quality of life (e.g., loss of libido and loss of muscle mass). *See* Declaration of Larry Norton M.D. ¶12. Thus, at best, the discovery of an optimal dose of a chemotherapeutic agent would make it obvious to try in a sequential and/or dose dense regimen. However, "'obvious to try' is not the standard under § 103." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

For the foregoing reasons, Applicant respectfully submits that currently pending claims 40-43, 45-69, 71-82 and 119-128 are unobvious in light of Hudis et al. and Henderson et al. and requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

Conclusion

In view of the remarks presented herein, it is respectfully submitted that the present application is in condition for final allowance and notice to such effect is requested. If the Examiner believes that additional issues need to be resolved before this application can be passed to issue, the undersigned invites the Examiner to contact him at the telephone number provided below. If there are any fees due, please charge any such fees to our deposit account No. 501561 and reference attorney docket number 93580.010100.

Respectfully,

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